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Mossbauer spectroscopy and magnetic moment measurements have been used in conjunction with electrochemical, pH, and optical spectroscopic measurements to study iron deposition and mobilization in mammalian and bacterial ferririn, and to study the structure of the iron containing cores of the proteins. Related aspects of magnetite biomineralization in bacteria were also studied.

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FINAL REPORT

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IRON REGULATION BY FERRITIN

PERIOD: JULY 1, 1985 - JUNE 30, 1988

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A. RESEARCH OBJECTIVES

The objectives of this research program have been to study the mechanisms of iron deposition, storage and mobilization in ferritin proteins, and to study related iron biomineralization processes in microorganisms.

B. RESEARCH SUMMARIES

1. Reduction of Mammalian Ferritin

Strategies for the biological storage of iron in such a way that it is available for metabolic needs, yet nontoxic, center on a widely distributed class of proteins, the ferritins. Ferritins are found in organisms as diverse as bacteria and mammals. Mammalian ferritin is a roughly spheroidal, 120Å diameter protein with a core of up to 4500 iron atoms in the 70Å diameter interior cavity. The protein shell is composed of 25 nearly identical subunits that are arranged to isolate the iron-containing core from the cellular environment. Six hydrophillic and eight hydrophobic channels provide access to the protein interior, presumably for electrons, protons and iron ions, and other small ions and molecules.

The ferritin iron core is a hydrous ferric oxide phosphate with nominal formula $(FeOOH)_8$ $(FeO \cdot H_2PO_4)$ and a structure similar to the protocrystalline mineral ferrihydrite, in which Fe^{3+} ions have six-fold oxygen coordination and oxygens are hexagonally close-packed. Iron is removed from the protein

slowly by Fe^{3+} chelators and more rapidly by reductants and Fe^{2+} chelators.

We have determined that mammalian ferritin (from horse spleen) can be reduced by up to one electron per iron atom with all iron retained in the protein cavity in the absence of iron chelators in the external medium. The redox reactions display a well defined decrease of the reduction potential with increasing pH, indicating that two protons are taken up with each electron during the reduction process. Mössbauer spectroscopy of partially reduced ferritin shows discrete Fe^{2+} and Fe^{3+} lines whose relative intensities are consistent with the degree of reduction. Partial reduction results in an increase of the superparamagnetic blocking temperature of the antiferromagnetically coupled Fe^{3+} component.

2. Binding of Fe^{2+} to Holoferritin

We have studied the binding of Fe^{2+} enriched to 90% in Fe-57 to holoferritin using Mössbauer spectroscopy. The experimental results can be summarized as follows: (a) Fe^{2+} binds to ferritin under anaerobic conditions; (b) the bound Fe^{2+} ions exchange electrons with the Fe^{3+} ions of the core: (c) the last added Fe^{3+} ions, those produced by oxidation of the originally added Fe^{2+} ions, are preferentially reduced when ferritin is incubated with a reductant such as dithionite.

The results imply that Fe^{2+} ions enter and are bound within the ferritin cavity. Since apoferritin binds ~12 Fe^{2+} ions per molecule, the binding of >100 Fe^{2+} ions by the holoprotein

implies many more binding sites, perhaps on the surface of the core. Binding on the surface of the core would also facilitate the exchange of electrons with the Fe^{3+} ions of the core. Since addition of Fe^{2+} ions produces a core that is spectroscopically indistinguishable from a core which is partially reduced electrochemically, redox states formed by partial reduction are thermodynamically as well as kinetically stable. Higher states of reduction, in contrast, may be only kinetically stable. the number of bound Fe^{2+} ions could depend on the average iron concentration per molecule, and because the reduction potential is pH dependent, on the pH of the medium.

3. Redox Reactivity of Mammalian and Bacterial Ferritins

Both mammalian and bacterial ferritin undergo rapid reaction with small molecule reductants, in the absence of Fe^{2+} chelators, to form ferritins with reduced (Fe^{2+}) mineral cores. Large, low potential reductants (flavoproteins and ferredoxins) similarly react anaerobically with both ferritin types to quantitatively produce Fe^{2+} in the ferritin cores. The oxidation of Fe^{2+} ferritin by large protein oxidants (cytochrome c and Cu(II) proteins) also readily occurs yielding reduced heme and Cu(I) proteins and ferritins with Fe^{3+} in their cores. These latter oxidants also convert enthetically added Fe^{2+}, bound in apo or holo mammalian or bacterial ferritin, to the corresponding Fe^{3+} state in the core of each ferritin type. Because the protein reductants and oxidants are much larger than the channels leading into the mineral core attached to the ferritin interior,

we conclude that redox reactions involving the Fe^{2+}/Fe^{3+} components of the ferritin core can occur without direct interaction of the redox reagent at the mineral core surface. Our results also suggest that the oxo, hydroxy species of the core, composed of essentially FeOOH, arise exclusively from solvent deprotonation. The long distance ferritin-protein electron transfer observed in this study may occur by electron tunneling.

4. Sequestration of Ferrous Iron by Mammalian Ferritin

Ferritin stores iron for plants, animals, and bacteria. The need for iron storage has been related to the accumulation of dioxygen in the terrestrial atmosphere and the oxidation of iron to insoluble ferric oxyhydroxides. We have found using Mössbauer spectroscopy that the protein coat of ferritin sequesters large amounts of ferrous iron, possibly as a ferrous oxyhydroxide precipitate inside the protein coat, oxidizing slowly over many hours. The results solve the problem of the massive electron flux predicted in cells such as macrophages, which recycle iron through ferritin in a short time; if the iron is not completely oxidized, it need only be solubilized rather than reduced and solubilized to be released from the protein. In addition, stabilization of ferrous iron by ferritin protein coats suggests a role in the metabolism of primitive organisms such as those reducing sulfate; ferritin may thus be among the oldest of proteins.

5. Redox Properties and Mössbauer Spectroscopy of *Azotobacter vinelandii* Bacterial Ferritin

The bacterial ferritin obtained from *Azotobacter vinelandii* differs in significant ways from mammalian ferritin even though both proteins have a number of properties in common. AV ferritin has a high phosphate content ranging from near 0.5 to 1.0 P_i/core Fe, values much higher than that of 0.1 P_i/Fe reported for mammalian ferritin. The increased stability of the Fe^{2+} core, the different redox properties and the greatly different proton-uptake capability observed suggest a significantly different core character compared to that in mammalian ferritin. The high phosphate level in the core matrix thus seems to be the determining factor for these differences in core behavior.

The presence of heme in bacterial ferritin raises a number of questions regarding its purpose and its relationship with the core. The quite constant stoichiometry of 0.5 heme/subunit suggests a relationship of 1 heme being shared between two subunits but the significance of this possibility remains unclear.

Related to the reducibility of the AV ferritin core is the question of concerted proton transfer. We have previously reported that the reduction of mammalian ferritin core Fe^{3+} is accompanied by the transfer of $2H^+/e$. This proton transfer was determined directly from pH measurements and from the decrease in core Fe^{3+} reduction potential with decreasing pH. No such reduction potential variation with pH was encountered with AV ferritin, except at pH 6.0, suggesting the lack of proton

involvement with core Fe^{3+} reduction. This demonstrates a significant difference between the core properties of AV ferritin and mammalian ferritin, a result also suggested by the high P_i content of the former relative to the latter. If the AV ferritin is indeed the analogous iron storage protein in bacteria, the results so far obtained suggest the method of Fe storage and release may differ significantly from those in the mammalian system.

Mössbauer spectroscopy of oxidized AV ferritin indicates that the cores consist of antiferromagnetically-coupled high spin Fe^{3+} which exhibit superparamagnetic behavior at low temperatures. In this respect AV ferritin is similar to mammalian ferritin, except that the average blocking temperatures are less in AV ferritin. This might reflect the higher phosphate/Fe3+ ratio and poorer crystallinity in AV ferritin. Reduction of AV ferritin results in Fe^{2+} in the core. Fe^{2+} and Fe^{3+} ions in partially reduced samples have different temperature dependences of their recoilless fractions, and different temperature dependences of their magnetic hyperfine interactions. Taken together with the apparent increase in the average Fe^{3+} particle size in the partially reduced samples, this suggests that Fe^{2+} ions form a separate phase in the AV ferritin cores, and that cores containing less iron atoms are preferentially reduced. The properties of reduced iron in AV ferritin are very similar to those of reduced iron in mammalian ferritin.

6. Magnetic Properties of Oxo-bridged Trinuclear Iron (III) Complexes of a Polyimidazole Ligand

Oxo-bridged polyiron centers are widespread in the mineralogical and biological worlds. Discrete binuclear centers occur in the oxygen transport proteins hemerythrin found in marine invertebrates, in ribonucleotide reductase, and in purple acid phosphates. Polynuclear iron centers, found in the iron storage proteins ferritin and hemosiderin, are also involved in the formation of magnetic crystals in magnetotactic organisms and chitons. As discrete units, oxo-bridged trinuclear iron centers are thus far unknown in biology, but are likely intermediates in the formation of larger polynuclear iron aggregates. The $[Fe_3O]^{7+}$ unit has been proposed as the smallest building block of the ferritin core.

Two procedures were used for preparing the novel trinuclear complex $[Fe_3O(TIEO)_2(O_2CPh)_2Cl_3]\cdot 2C_6H_6$. An X-ray crystallographic study of this complex revealed an isosceles triangle of iron atoms with a triply bridging oxo atom nearly in the plane of the triangle. The structure of the $[Fe_3O]^{7+}$ core consists of two short Fe-O bonds and one long one. The coordinating spheres of the equivalent iron atoms, Fe(1) and Fe(2), are composed of two imidazole nitrogen atoms, the briding oxo atom, a bridging alkoxide oxygen atom of the TIEO- ligand, an oxygen atom of a bridging benzoate ligand, and a terminal chloride ion. The two benzoate, two alkoxide, and μ-oxo groups bridge to Fe(3), which has a terminal chloride ligand to complete its coordination sphere. Two N-methyllimidazole groups, one from each ligand, are

not coordinated. From magnetization studies the ground state of $[Fe_3O(TIEO)_2(O_2CPh)_2Cl_3]$ is found to be S = 5/2, in contrast to the classical basic iron (III) carboxylates, which contain symmetrically bridged $[Fe_3O]^{7+}$ cores having S = 1/2. Variable temperature magnetic susceptibility measurements were fit to a theoretical expression derived from a spin Hamiltonian taking into account two different exchange pathways along inequivalent sides of the isosceles triangle. The analysis yielded J_{12} = -55(1) cm^{-1} and $J_{13} = J_{23}$ = -8.04 cm^{-1}, with the larger antiferromagnetic coupling interaction occuring between iron centers linked by the shortest μ-oxo bridge bonds. Mössbauer isomer shift and quadrupole splitting parameters at 4.2 K are δ = 0.48 and 0.52 mm/sec and ΔEQ = -1.16 and 0.74 mm/sec for Fe(1) [= Fe(2)] and Fe(3), respectively. In external magnetic fields at 4.2 K there are two magnetic subsites with $H_{hf}(1) = H_{hf}(2) = 0$ and $H_{hf}(3)$ = -540 kOe, corresponding to Fe(1) and Fe(2) with local spin $|S_z> = 5/2$. This result confirms the $|S_t = 5/2, S_p = 0>$ ground state of the cluster. These results were compared and contrasted with structural, magnetic, and spectroscopic data for μ-oxodiiron(III), μ-hydroxodiiron(III), and symmetric μ_3-oxotriiron(III) cores which, like the present asymmetric μ_3-oxotriiron(III) core, are ubiquitous in mineralogy and biology.

7. Synthesis, Structure, and Properties of an Undecairon(III) Oxo-hydroxo Aggregate: An approach to the polyiron core in Ferritin

A novel, discrete undecairon(III) oxo-hydroxo aggregate, $[Fe_{11}O_6(OH)_6(O_2CPh)_{15}]$, has been synthesized by controlled hydrolytic polymerization in nonaqueous solvents of simple mononuclear and oxo-bridged binuclear ferric salts. The complex was structurally characterized in two crystalline forms. In the rhombohedral form, $[Fe_{11}O_6(OH)_6(O_2CPh)_{15}]\cdot 6THF$, the molecules have crystographically required D_3 symmetry. The eleven-iron atoms define a twisted, pentacapped trigonal prism. Two type A iron atoms located on the three fold symmetry axis are joined by μ_3-oxo bridges to six type B iron atoms at the corners of the twisted trigonal prism. These type B iron atoms are linked to one another and to three type C iron atoms, situated on twofold symmetry axes, by μ_3-hydroxo bridges. A sheath of 15 bidenate bridging benzoate ligands, no two of which join the same pair of iron atoms, completes the pseudooctahedral coordination about each of the 11 high spin ferric centers. The Fe-O bond lengths range from 1.876 (5) Å for Fe-(μ-oxo) to 2.106 (8) Å for Fe-O(benzoate) type interactions. The six tetrahydrofuran molecules penetrate the sheath of benzoate ligands to form hydrogen bonds to protons on the six μ_3-hydroxo ligands. The other crystalline form, $[Fe_{11}O_6(OH)_6(O_2CPh)_{15}]\cdot H_2O\cdot 8MeCN$, is triclinic and has no imposed molecular site symmetry. The molecular geometry of the undecairon(III) aggregate, however, is nearly identical with that in the rhombohedral form. Solutions of $[Fe_{11}O_6(OH)_6(O_2CPh)_{15}]$ in

dry Ch_2Cl_2 or CH_3CN are indefinitely stable, judging by optical spectroscopy. Cyclic voltammetric studies in the former solvent revelaed a quasi-reversible one-electron reduction at $E_{1/2}$ = -0.309 V vs. SCE, tentatively assigned to the formation of $[Fe_{11}O_6(OH)_6(O_2CPh)_{15}]^-$, as well as two irreversible waves with peak currents as -0.817 and -1.323 V. The temperature-dependent magnetic susceptibility behavior of the undecairon(III) aggregate is consistent with a ground state spin S_T = 1/2 per aggregate and internal antiferromagnetic coupling. High-field magnetization and Mössbauer experiments reveal that the individual Fe_{11} molecules have incipient magnetic order with very low anisotropy and some exchange interactions on the order of 10 cm^{-1}. The presence of μ_3-oxo, μ_3-hydroxo, and carboxylate ligands, as well as the manner in which $[Fe_{11}O_6(OH)_6(O_2CPh)_{15}]$ self-assembles, make it an attractive model for the polyiron core in ferritin.

8. Magnetic Properties of Magnetosomes in *A. magnetotacticum*

The magnetic properties of magnetosomes in the freshwater magnetotactic bacterium *Aquaspirillum magnetotacticum* have been determined. The magnetosomes are well crystallized particles of magnetite with dimensions of 40 to 50 nm, which are arranged within cells in a single linear chain, and are within the single-magnetic-domain (SD) size range for magnetite. A variety of magnetic properties have been measured for two samples of dispersions of freeze-dried cells consisting of (1) intact cells (M-1) and (2) magnetosome chains separated from cells (M-2). An important result is that the acquisition and demagnetization of

various type of remanent magnetizations are markedly different for the two samples and suggest that remanence is substantially affected by magnetostatic interactions. Interactions are likely to be much more important in M-2 because the extracted magnetosome chaine are no longer separated from one another by the cell membrane and cytoplasm. Other experimental data for intact cells are in agreement with predictions based on the chain of spheres model for magnetization reversal, which is consistent with the unique linear arrangement of equidimensional particles in A. *magnetotacticum.* The magnetic properties of bacterial and synthetic magnetites have also been compared and the paleomagnetic implications of this study discussed.

9. Anaerobic Magnetite Production by a Marine, Magnetotactic Bacterium

Bacterial production of magnetite represents a significant contribution to the natural remanent magnetism of deep-sea and other sediments. Because cells of the freshwater magnetotactic bacterium, *Aquaspirillum magnetotacticum,* require molecular oxygen for growth and magnetite systhesis, production of magnetite by magnetotactic bacteria has beer considered to occur only in surficial aerobic sediments. Moreover, it has been suggested that deposits of single-domain magnetite crystals are paleooxygen indicators, presumably having been formed under predominantly microaerobic conditions. In contrast, some nonmagnetotactic, dissimilatory iron-reducing bacteria, produce extracellular magnetite from hydrous ferric oxide under anaerobic

conditions. We have isolated and axenically cultured a marine, magnetotactic bacterium, designated MV-1, that can synthesize intracellular, single-domain magnetite crystals under strictly anaerobic conditions. We conclude that magnetotactic bacteria do not necessarily require molecular oxygen for magnetite synthesis and suggest that they, as well as dissimilatory iron-reducing bacteria, can contribute to the natural remanent magnetism of even long-term anaerobic sediments.

10. Intercellular Membrane Fusions in a Multicellular Magnetotactic Prokaryote

Fossil records of the first two billion years of life on Earth reveal that the first cells identifiably preserved in rocks were prokaryotic. The evolution of eukaryotes, commencing about 1.4 billion years ago, was associated with increases in both the size and structural complexity of organisms. Many extant eukaryotic species are multicellular and possess a tissue form of organization. The integrity of tissues is maintained by such specialized intercellular connections as tight junctions (the zonula occuludens, zonula adherens and macula adherens or desmosome, in association with microfilaments) and gap or nexus junctions; all of which differ in structure and function. The nexus consists of regions in which adjacent cells are held together with intact cytoplasmic membranes separated by a constant gap of 2 nm. These gap junctions between epidermal, muscle and nerve cells may serve as low resistance pathways for ion conduction and coordinate function among cell groups in

eukaryotes. We have found by electron microscopy that the cells of a multicellular, magnetotactic prokaryote common in marine nearshore, pond and lagoon sediments possess fused membranes similar to membrane junctions between cells comprising eukaryotic tissues. This is the first report of a multicellular prokaryote with fused membranes. It suggests that multicellularity in prokaryotes could have predated that in eukaryotes.

11. Magnetotactic Algae

In addition to prokaryotic microorganisms, Fe_3O_4 has been identified in magnetotactic euglenoid algal cells from brackish sediments in Brazil. TEM of these organisms shows that they contain numerous Fe_3O_4 particles arranged in chains, oriented more or less parallel to the long axis of the cell. Individual particles are arrowhead or tooth-shaped and are within the single-magnetic-domain size range for Fe_3O_4. Hence, each chain is a permanent magnetic dipole. If the moments of all the chains were oriented parallel to each other, a cell would have a magnetic dipole moment equal to the sum of the moments of all its particles. An estimate of the total magnetic moment M of algal cells gives $M = 5 \times 10^{-10}$ emu. This is about 1000 times the moment of a typical magnetic bacterium, and corresponds to a total of about 3×10^3 aligned particles of the observed dimensions.

The biological significance of magnetotaxis in these algae is not yet understood. However the highly ordered arrangement of the chains of particles in the cells suggests that they are chains of magnetosomes very much like the chains of magnetosomes

in bacteria. Evidence for the presence of membranes enveloping the particles must await TEM of this sections. However, the fact that the particles are separated from each other and not clumped is evidence that they are not free to move in the cells. Chains of free magnetic particles would lower their energy by moving together and eventually forming clumps.

Of especial biological interest is the fact that these eukaryotic organisms possess magnetosomes that are similar if not identical to those in prokaryotes. This indicates that similar products of gene expression occur in representatives of both major groups of organisms.

12. Hydrodynamic Coupling and Band Formation by Swimming Magnetotactic Bacteria

An unusual migration phenomenon occurs in dense suspensions of unidirectional magnetotactic bacteria swimming in narrow bore glass tubes when subjected to magnetic fields. Instead of the bacteria travelling down the tube in a cloud that disperses with time owing to the continuous distribution of swimming speeds in the population, the cells form stable, migrating waves or bands that translate with their long axes perpendicular to their common direction of motion. The number of bacteria in a band is variable, up to several thousand, and cell separations generally approximate five body diameters. Small 'protobands' or lateral strings, consisting of as few as two or three cells, are also observed. Cells within a given band migrate at the same speed, but different bands move at different speeds; that is, band

formation is accompanied by velocity sorting of the bacteria in the population. Cells within a given exhibit complex local motions, in addition to which their positions within the band appear to change continually; yet the band itself remains stable for relatively long times. Reversing the direction of the magnetic field in the tube causes the bands to break up, subsequently reform, and migrate in the opposite direction, with the faster bands, initially behind the slower ones, catching up and eventually moving to the force.

We have analyzed the quasistatic hydrodynamic forces existing between two proximate swimming bacteria in a viscous fluid. The additional hydrodynamic force and torque on a given cell due to a near neighbor was computed. The calculation demonstrated that hydrodynamic coupling results in a lateral attraction that could account for band formation.

Essentially, the position at which a cell exerts retarding drag forces on the fluid is displaced ahead of that where it exerts propulsive forces on the fluid. This displacement of forces generates a Stokes-doublet-like flow far from the body, causing forces to be exerted on nearby cells; these hydrodynamic forces attract side-by-side neighbors and repel head-to-tail neighbors. Globally, this tends to arrange cells into side-by-side configurations, forming long, this, bands lying perpendicualr to their common direction of motion.

Although hydrodynamic coupling of the type considered produces especially dramatic effects upon magnetotactic bacteria, it should be equally operative in dense suspensions of other flagellated bacteria. However, the biased random walk of chemotactic bacteria, with periodic reversals of the direction of flagellar rotation, would appear to prevent formation of stable bands. Nevertheless, hydrodynamic coupling might result in local density fluctuations or correlated cellular motions within the suspension.

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